REMARKS

Reconsideration of this application is requested.

The restriction requirement of Group I and Group II-III has been made FINAL. Accordingly, non-elected claims 7, 13, and 14 remain withdrawn from consideration by the Examiner. However, Applicant reserves the right to prosecute the non-elected subject matter in a divisional patent application.

Applicant acknowledges the Examiner's inclusion of the additional elected species defined by SEQ ID NOS: 6, 7, 9, 10, and 12-20.

Claims 1-6, 8-12, and 15-16 have been pending in this application. Claims 1-5, 7, 8, 9, 13 and 14 have now been cancelled without prejudice.

In place of the cancelled claims, Applicant has introduced the new claims 17-22, in order to more clearly define the scope of the invention. No new matter was introduced with this amendment as the claims are completely supported by the instant Specification.

Thus, claims 6, 10-12, and 15-22 are now pending.

Claims 6, 10, 11, 12 and 15 have been amended to depend from the new main claim 17. Claim 17 is an amended independent form of claim 4, directed to a synthetic immunogen for inducing specific antibodies against GnRH comprising a promiscuous helper T-lymphocyte epitope fused through a spacer peptide to a GnRH-immunomimic peptide comprising either an amino acid sequence SEQ ID NO: 1, or a 2-10 amino acid sequence portion of SEQ ID NO: 1.

Newly added independent claim 21 is directed to a combination or composition of the combination so that the GnRH immunomimic peptide is associated with several distinct T-L-epitopes in the mixture encompassing any of SEQ ID NOS 9-20. Pharmaceutical composition

claim 22 has been newly added to include at least two different synthetic immunogen sequences, as defined in claims 11, 12, or 21.

The scope of the claimed subject matter is supported by the instant description, particularly on pages 14 and 16.

Claims 1-6, 8-12 and 15-16 are rejected under 35 U.S.C. § 112, first paragraph, as only enabling for a synthetic immunogen for inducing specific antibodies against GnRH comprising a fusion peptide wherein the synthetic immunogen is selected from the group consisting of SEQ ID NO: 9-20. The Examiner contends that the examples involving SEQ ID NOS: 9-20 are not sufficient to enable one of ordinary skills to practice the invention as originally claimed in claims 1 and 2.

Applicant disagrees. In view of the cancellation of claims 1-5, and 8 and 9, the rejection of these claims under the statute as detailed on pages 3-7 of the Action, is deemed moot. Moreover, Applicant believes the instant description of different helper T-cell epitope peptides that are contiguous through a variety of spacer peptides with a GnRH-immunomimic peptide comprising either the 1-10 amino acid sequence and/or partial 2-10 amino acid sequence, (see page 7 of the Specification), clearly lays the foundation for the practitioner to construct commensurate immunogenic fusion peptides against GnRH.

Applicant further believes that the newly added claim 17 overcomes the rejection of original claim 4 under Section 112, first paragraph, in that the Specification fully supports the invention as presently claimed. The examples show the feasibility and efficacy of synthetic immunogenic peptide fused through an appropriate spacer peptide to a GnRH-immunomimic peptide unexpectedly comprising either a whole 1-10 aa GnRH sequence and/or a partial 2-10 aa GnRH sequence. No undue experimentation by one of ordinary skill in this art would be

necessary for any immunogenic constructs within the claimed scope. In view of the present amendment, Applicant asserts that the claimed invention provides sufficient examples of a broad variety of fusion peptides for inducing specific anti-GnRH antibodies.

Moreover, the term "comprising" is appropriate since it would be understood not to exceed the scope of the invention as described in the instant disclosure.

Claims 1-6, 8-12 and 15-16 are rejected under 35 U.S.C. § 112, first paragraph, as claiming subject matter scope which is allegedly not supported by the Specification. As detailed by the Examiner on pages 8 and 9 (top paragraph), the invention allegedly does not predict any scope beyond the SEQ ID NOS: 9-20.

Applicant disagrees. In the first instance, the rejected subject matter of claims 1-5, 8 and 9 has been cancelled without prejudice and is therefore deemed moot. Secondly, the presently proposed new main claim 17 as well as the claims dependent therefrom overcome this rejection. In particular, claim 17, replacing claim 4, is based on the description on pages 6 and 7 of the Specification and the examples, such that the skilled practitioner would have sufficient instruction for producing an effective immunogenic peptide analogue using, for example, different permutations of the various epitopes and sequences described herein without undue experimentation. The relevant technology of peptide synthesis is well within the knowledge and ability of the non-inventive skilled practitioner. Applicant asserts that not every possible permutation of this invention can be described by example in view of the obvious limitations of time and money. Therefore, the presently claimed invention is deemed fully supported by the instant Specification. Moreover, the rejection of the claims 10-12 and 15, now amended to depend directly or indirectly from new claim 17, should be withdrawn, which action is solicited.

Claims 4 and 5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner contends that "a whole or partial sequence of GnRH of SEQ ID NO: 1" of claim 4 is ambiguous because SEQ ID No: 1 is allegedly only a partial sequence of the GnRH.

Applicant disagrees. In the first instance, new claim 17, the amended successor to claim 4, distinctly defines the respective GnRH sequences involved. Secondly, contrary to the Examiner's opinion, the GnRH sequence of SEQ IS NO: 1 is not partial but complete. As disclosed in the instant Sequence Listing, GnRH can have terminal modifications, such as a pyroglutamic acid in position one and an amidated glycine in position ten. Thus the GnRH sequence of SEQ ID NO: 1 is completely described. In addition, the GnRH sequence is disclosed in co-assigned US 5,688,506, which disclosure has been incorporated entirely herein by reference.

The rejection of cancelled claim 5 is deemed moot, and should be withdrawn.

Claims 1-2, 8 and 15 are rejected under 35 U.S.C. § 102(b), as anticipated by the reference to Ghosh et al. ("Ghosh") (International Immunology 11(7) : 1103-1110, 1999). The Examiner alleges that the Ghosh reference discloses a synthetic immunogen for inducing specific antibodies against GnRH comprising a fusion peptide of promiscuous helper T peptide epitope such as Th 1 epitope from tetanus toxin (T1) or various Th 1 epitopes from E. coli (T2 and T3) fused to the amino terminus or the carboxy terminus of GnRH immunomimic peptides.

Applicant disagrees. The cited reference neither discloses nor suggest the presently claimed immunogen. In the first instance, the present amendment has cancelled the rejected claims 1-2 and 8 without prejudice. Their rejection is therefore rendered moot. Moreover, claim 15 has been amended to depend from new claim 17. Moreover, the cited Ghosh

reference does not even resemble the invention as presently claimed. The reference does not disclose the instant invention wherein the synthetic peptide according to claim 17 (amended from former claim 4) comprises a helper T-lymphocyte epitope polypeptide is fused through an intervening spacer peptide to a GnRH immunomimic peptide which contains the whole GnRH 1-10 aa sequence and/or a partial GnRH 2-10 aa as discussed above.

In as much as cancelled claim 4 has been found free of the art, the newly added independent claim 17 as amended replacement of claim 4, as well as the amended dependent claim 15 are also deemed free. Therefore, Applicant requests withdrawal of this rejection under 35 U.S.C. § 102(b).

Claims 1-3, 5-6, 8-9, and 15 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 94/25060 ("GG"). The GG reference allegedly discloses an immunogen for inducing anti-GnRH antibodies, wherein the fusion peptide is constructed from helper T cell epitopes fused through a spacer peptide to a whole GnRH peptide. Specifically, the Examiner contends that the instant invention would comprise, i.e. add, the additional amino acids of the cited reference.

Applicant disagrees. The cited reference neither discloses nor suggests the invention as presently claimed. The claims 1-3, 5, 8, and 9 have been cancelled without prejudice; and pending claims 6 and 15 have been amended to depend from new claim 17. As set forth above, the inventive scope of original claim 4 has been further defined by the new main claim 17 which has replaced claim 4. As original claims 4 and 10-12 were free of the art, successor claim 17 and amended dependent claims 10-12 are also deemed free of the art.

The other pending claims, directly or indirectly dependent from claim 17, are also deemed to be free of the cited GG reference.

Claims 1-3, 5, 8-9 and 15 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S 5,837,268 to Potter et al. ("Potter '268").

Applicant disagrees. The cited reference neither discloses nor suggests the claimed invention. In the first instance, rejected claims 1, 2, 3, 5, 8 and 9 have been cancelled without prejudice. This rejection is therefore deemed moot. Secondly, rejected claim 15 has been amended to depend from new claim 17 which replaces and more distinctly defines the inventive scope of the cancelled original claim 4, which has been found free of the art. Amended claim 15 is therefore also deemed free of the cited reference to Potter '268.

Newly added independent claim 21, which is directed to the combined immunogens, SEQ ID NOS: 10 and 11, is also believed free of the cited references. New claim 22 has been added to provide a pharmaceutical composition as injectable of at least two of the immunogens claimed by claims 11, 12, or 21. No new matter has been introduced with these claims which are supported by the instant Specification on page 14, Table 1, Immunogen J.

The presently proposed amendment of the Specification includes the added sentence in the Summary on page 5, copying the scope embodiment claimed in original pending claim 10. No new matter has been introduced since the subject matter of claim 10 is of record and further supported by the description on page 16, lines 10 and 11. A substitute page 5 containing the amendment is attached hereto.

On page 6 of the Specification, the inadvertent typographical errors concerning the SEQ ID NOS of the helper T-cell epitopes of tetanus toxoid peptide and malarial CSP peptide have been corrected by this amendment. No new matter has been introduced as the correct identification numbers have been of record in the instant Sequence Listing. A substitute page 6 containing the corrections is attached hereto.

Applicant has made a good faith effort to place the application in condition for allowance, which favorable action is solicited.

The Commissioner is authorized to charge any fee which may be due in connection with this response to Deposit Account No. 23-1703.

Dated: February 24, 2003

Respectfully submitted,

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Enclosure

AMENDMENT: Version with Markings to Show Changes Made, I.

IN THE SPECIFICATION:

2. Promiscuous Th-epitope moieties from measles virus protein F (MSF) (sequence 288-302 aa, SEQ ID NO: 8), tetanus toxoid (TT) (sequence 947-967 aa, SEQ ID NO: [9] 4, or sequence 830-844 aa, SEQ ID NO: [10] 2) and malaria Plasmodium falciparum CSP protein (sequence 378-398 aa, SEQ ID NO: [11] 3) are used in these constructs.

AMENDMENT: Version with Markings to Show Changes Made, II.

IN THE CLAIMS:

6. (Amended) The synthetic immunogen of claim [5] 17 wherein the promiscuous epitope is selected from the group consisting of a sequence of TT, DT, Malarial Protein CSP, and MSP-F.

10. (Amended) The synthetic immunogen of claim [9] 17 wherein the spacer peptide is selected from the group consisting of Gly-Pro-Ser-Leu (SEQ ID NO: 5 in the Sequence Listing), Ser-Ser-Gly-Pro-Ser-Leu (SEQ ID NO: 6 in the Sequence Listing), and Ser-Ser-Gly-Pro-Ser-Leu-Lys-Leu (SEQ ID NO: 7 in the Sequence Listing).

11. (Amended) The synthetic immunogen of claim [1] 17 wherein the fusion peptide is selected from the group consisting of the peptide defined by SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

12. (Amended) The synthetic immunogen of claim [1] 17 wherein the fusion peptide is selected from the group consisting of one or more than one peptide defined by SEQ ID NO: 10 and SEQ ID NO: 11.

15. (Amended) A pharmaceutical injectable composition comprising the synthetic immunogen as claimed in claim [1] 17, and a pharmaceutically acceptable carrier.

Pending Claims of Serial No. 09/848,834

17. A synthetic immunogen for inducing specific antibodies against GnRH comprising a promiscuous helper T-lymphocyte epitope fused through a spacer peptide to a GnRH immunomimic peptide comprising either a whole amino acid sequence of SEQ ID NO: 1, or a partial 2-10 amino acid sequence of SEQ ID NO: 1.

18. The synthetic immunogen of claim 17 wherein the helper T-lymphocyte epitope is fused through a spacer peptide to the amino-terminus and/or carboxy-terminus of the GnRH-immunomimic peptide.

19. The synthetic immunogen of claim 17 wherein the promiscuous helper T-lymphocyte epitope is fused through a spacer peptide to the amino-terminus of the GnRH-immunomimic peptide.

20. The synthetic immunogen of claim 17 comprising an acetylated amino-terminus and/or an amidated carboxy-terminus.

6. The synthetic immunogen of claim 17, wherein the promiscuous epitope is selected from the group consisting of a sequence of TT, DT, Malarial Protein CSP, and MSP-E.

10. The synthetic immunogen of claim 17 wherein the spacer peptide is selected from the group consisting of Gly-Pro-Ser-Leu (SEQ ID NO: 5 in the Sequence Listing), Ser-Ser-Gly-Pro-Ser-Leu (SEQ ID NO: 6 in the Sequence Listing), and Ser-Ser-Gly-Pro-Ser-Leu-Lys-Leu (SEQ ID NO: 7 in the Sequence Listing).

11. The synthetic immunogen of claim 17 wherein the fusion peptide is selected from the group consisting of the peptide defined by SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

Pending Claims of Serial No. 09/848,834 (continued)

12. The synthetic immunogen of claim 17 wherein the fusion peptide is selected from the group consisting of one or more than one peptide defined by SEQ ID NO: 10 and SEQ ID NO: 11.

15. A pharmaceutical injectable composition comprising the synthetic immunogen as claimed in claim 17, and a pharmaceutically acceptable carrier.

16. A pharmaceutical injectable composition comprising the synthetic immunogen as claimed in claim 12, and a pharmaceutically acceptable carrier.

21. A combination of synthetic immunogens for inducing specific antibodies against GnRH comprising:

(i) a fusion peptide as defined by SEQ ID NO: 10; and

(II) a fusion peptide as defined by SEQ ID NO: 11; so as to store and use it separately or in a mixture.--

-22. A pharmaceutical injectable composition comprising at least two different synthetic immunogens of anyone of the claims 11, 12 and 21, and a pharmaceutically acceptable carrier.

SUMMARY OF THE INVENTION

The present invention provides immunogens comprising a chimeric peptide of a hormone-immunomimic peptide epitope fused in sequence with an immunogenic epitope. The hormone-immunogenic peptide can be fused either directly to or through a spacer sequence to an immunogenic peptide epitope.

These fusion peptides combine at least one epitope of a target substance which may be non immunogen in its natural state with at least one immunogenic peptide sequence of suitable immunogenic proteins. The sequences of both target epitope and immunogen may be selected from the amino-terminal or carboxy-terminal region or both. A peptide also can be synthesized from the internal region of the peptide or protein. The fusion product may be acetylated at the amino-terminal end and amidated at the carboxy-terminal end of the peptide sequence. An embodiment of the invention provides a synthetic immunogenic fusion peptide selected from the group consisting of one or more than one peptide defined by SEQ ID NO: 10 and SEQ ID NO: 11.

An embodiment of the invention provides an anti-GnRH immunogen chimeric peptide construct comprising a suitable immunogenic epitope, such as, *e.g.*, short peptide sequences selected from the measles virus protein F (MVF), tetanus toxoid (TT), or malaria plasmodium falciparum CSP protein. The invention also provides for methods of immunization with a composition comprising a chimeric peptide with one or more GnRH epitopes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the mean Anti-GnRH antibody titers obtained from rabbits using chimeric anti-GnRH Immunogens A through J, and as controls, Immunogens K and L as well as conjugate immunogen C, GnRH:DT; and

Figure 2 illustrates the relationship between gross muscle reaction score and mean anti-GnRH Antibody Titer on GnRH Chimeras and Controls.

DETAILED DESCRIPTION OF THE INVENTION

Chimeric peptides comprising GnRH mimicking epitopes have been constructed and useful in generating improved antibody titers.

Since self-antigen epitopes of gonadotropin releasing hormone (GnRH) are not inherently immunogenic the immune response may be aided by immunogenic constructs according to the invention wherein a target peptide epitope is located on the same synthesized peptide as is an immunogenic peptide epitope.

Several different chimeric peptides are described in Example 1.

EXAMPLE I

The peptide sequences combine a select promiscuous T-helper-epitope through an inserted short spacer peptide (e.g., 4-8 amino acids) with at least one target hormone peptide. Suitable spacers of this invention include but are not limited to the peptides comprising the following amino acid sequence, GPSL (see SEQ ID NO: 5); SSGPSL (SEQ ID NO: 6); and SSGPSLKL (SEQ ID NO: 7), which are inserted in the peptide chimera to isolate the three dimensional folding of the immunogenic peptide from that of the hormone peptide.

Promiscuous Th-epitope moieties from measles virus protein F (MSF) (sequence 288-302 aa, SEQ ID NO: 8), tetanus toxoid (TT) (sequence 947-967 aa, SEQ ID NO: 4, or sequence 830-844 aa, SEQ ID NO: 2) and malaria Plasmodium falciparum CSP protein (sequence 378-398 aa, SEQ ID NO: 3) are used in these constructs. The hormone immunomimic epitopes were attached to the N-terminal or the C-terminus of the spacer as shown below. All mammalian GnRH peptides including the human hormone, have the same sequence. The GnRH hormone immunomimic epitope sequence comprises 1-10 amino acids of mammalian GnRH when attached